IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Donald L. Wise, Debra J. Trantolo, David D. Hile, and Stephen A. Doherty

Serial No.: 10/613,975 Art Unit: 1645

Filed: July 3, 2003 Examiner: Khatol Shahnan-Shah

For: *VACCINES TO INDUCE MUCOSAL IMMUNITY*

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Appellants request reinstatement of the previous Appeal, a notice of appeal having been filed November 6, 2006, and the Appeal Brief having been filed January 8, 2007. A new Notice of Appeal is enclosed and it is requested that payment of the fee be transferred to the current appeal. With only very minor differences, the same issues are present in the office action rejecting claims 1 and 3-11 mailed August 7, 2006, in the above-identified patent application, as in the office action mailed August 7, 2006, and in the office action mailed November 3, 2004. PLEASE NOTE THAT THIS IS THE THIRD APPEAL BRIEF FILED IN THIS APPLICATION. The examiner has also failed to act in a timely manner in the case. It is urgently requested that this case be allowed to proceed on appeal or be allowed. By failing to do so, or allowing the case, the examiner is being allowed to deprive the appellants of patent term. The Commissioner was originally authorized to charge the fee for filing the Appeal Brief for a

large entity, to Deposit Account No. 50-3129, so no additional fee should be required. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Depuy Mitek, a Johnson & Johnson company, this is assignee.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

However, it should be noted that this is the third appeal brief filed in this case, on basically the same issues, without an examiner's answer having been received.

(3) STATUS OF CLAIMS

Claims 1 and 3-11 are pending and on appeal. Claims 2 and 12-21 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in an amendment filed on January 4, 2007, in response to the office action mailed on August 7, 2006. In a telephone call with the examiner on January 8, 2007, and confirmed in the office action mailed May 18, 2007, the examiner indicated that this amendment would be entered.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof. Support for claim 1 can be found in the specification at least at page 8, lines 5-6, 16-18, and 20; at page 11, lines 1-2; page 20, lines 10-11; page 10, lines 26-27; page 25, lines 17-20 and claim 1 as originally filed. The composition defined by claim 3 comprises a mucoadhesive polymer coating (see at least page 25, lines 17-20), or an enteric outer coating or capsule (see at least page 20, lines 28-31) as required by claim 4.

As defined by claim 5, the composition has a particulate diameter of less than five microns (see at least page 8, lines 12-13). Claim 8 defines the polymer as a low molecular weight poly(D,L-lactide-co-glycolide) (see at least page 8, lines 3-5).

Claim 9 requires the pathogen be selected from the group consisting of *Plasmodium falciparum, Francisella tularensis, Bacillus anthracis*, and *Helicobacter pylori* (see page 7, lines 9-12). Claim 10 requires the composition also contain an adjuvant (see at least page 23, lines 9-10). Claim 11 specifies that the antigen is expressed or released for a period of weeks to months (see at least page 8, lines 13-16).

Claim 6 is a product by process claim. As defined by claim 6, the composition is formed by lyophilizing a solution of a biodegradable polymer to form an open-celled polymeric foam of approximately 95% void volume (see at least page 8, lines 5-6), impregnating the foam with an

aqueous solution of the nucleic acid (see at least page 8, lines 6-7, lyophilizing the foam to remove the water (see at least page 8, lines 7-8, and extruding the resulting matrix at ultrahigh pressures (see at least page 8, line 8). As defined by claim 7, the method also contains the step of cryogenically grinding the matrix of claim 1 to an average particle size of fifteen microns in diameter; and sieving to isolate particles less than five microns in diameter (see at least page 8, lines 10-13).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1 and 3-11 are enabled as required by 35 U.S.C. § 112, first paragraph.

(2) whether claims 1 and 3-11 are definite as required by 35 U.S.C. § 112, second paragraph.

(3) whether claims 1, 3-5, and 8-11 are obvious in view of O'Hogen. *J. Pharm. Pharmacol.*, 50(1):1-10 (1998) ("O'Hagan"), in view of U.S. Patent No. 6,689,608 to Mikos, et al. ("Mikos).

(7) ARGUMENT

(A) The Invention

Mucous membranes are the primary routes of entry for a large number and wide variety of disease carrying agents. Many pathogens enter and replicate at the mucosal surface before causing systemic infection. The mucosal immune system can be stimulated by oral administration. However, the induction of mucosal immunity has been shown to depend on a

number of variables including the delivery system. Local administration of antigens usually requires large amounts of antigen to produce a response (*See* the specification at least at page 9). As stated at page 9, delivery of antigen is key to developing an immune response and under-stimulation may fail to prime the immune system. The present application relates to effective and long-lasting vaccines incorporating nucleic acid encoding antigen, such as plasmid DNA, by encapsulating the DNA within a mucoadhesive controlled release particulate formulation.

As discussed at least at page 17, administration of naked DNA leaves the vaccine vulnerable to attack by enzymes that can reduce the half-life to minutes or hours. Chemical modification can increase the half life of the DNA vaccines, but this may also increase systemic toxicity and increases cost. Vaccines, including DNA vaccines, have been widely available for a long time. However, no one has put them into a mucoadhesive controlled release particulate formulation as claimed herein. As discussed at least at page 8, the mucoadhesive controlled release particulate formulation protects the antigen and stimulates and maintains the immune response to pathogens.

(B) Rejections under 35 U.S.C. § 112, first paragraph, enablement

Claims 1 and 3-11 were rejected as non-enabled as too broad with respect to the antigen. The examiner has acknowledged at page 2 that claims 1, 3-11 are enabled for a mucoadhesive controlled release particulate delivery system inducing immunogenic response against certain pathogens (Malaria and Anthrax).. The examiner provides no explanation why, if the composition is enabled for these two widely disparate pathogens, one an intracellular parasite and the other a bacteria, are not predictive of other pathogens. The basis of the rejection is that

appellants have not shown there there is a correlation between in vitro and in vivo studies are that there are animal models that correlate to efficacy in a human. The examiner has cited that there are problems in DNA vaccine work. However, no where is there an explanation of how the claims are enabled for two organisms but not others.

The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) described the legal standard for enablement under 35 U.S.C. § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the

quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. See *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). The adequacy of a specifications description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). There is no requirement for examples.

Analysis

Claims 1, 5, and 8 are enabled

The claims define compositions providing controlled release of DNA vaccines. The claims require encapsulation of nucleic acid encoding an antigen eliciting an immune response to a pathogen in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof. DNA encoding antigen is encapsulated into a mucoadhesive controlled release particulate formulation to achieve sustained delivery of the vaccine and to maintain an immune response.

As noted above, the examiner has conceded that the specification enables a skilled artisan to make and use the claimed vaccine formulation, but only if limited to two specific, if totally different, pathogens. The examiner provides no basis for this position, but rambles on about the breadth of the claims, the uncertainty in the field of DNA vaccines, ad the need for experimentation.

However, once one has acknowledged that the specification is enabling for malarial and anthrax vaccines, one must then ask the question why the specification is not enabling for other pathogens. The pathogens and antigens are known in the art. What Appellants disclose is a composition that enables sustained delivery of known antigens. In response, the Examiner cited to Ellis, "*New Technologies for Making Vaccines*" in Vaccines, Plotkin S.A., et al (eds), WB Sanders Company (Philadelphia) (1988) pp 568-671 ("Ellis") as evidence, that it is well recognized in the art that it is unclear whether antigens derived from a pathogen will elicit immunity, specifically citing to Ellis, page 571, 2nd full paragraph, where it is stated that "the key

problem of vaccine development is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies… and thus protect the host against attack by the pathogen". Ellis does not refute Appellants' statement that pathogens and antigens are known in the art. Appellants agree with the statement in Ellis, that the component of the pathogen that can elicit immune response has to be identified; this does not mean that such components have not been identified. In fact, Ellis goes on to discuss successful use of rDNA technology to develop vaccines for humans (See Ellis, page 571, from left col. 3rd paragraph to right col. 2nd paragraph). The specification at least at page 11, lines 1-3 states that the antigen is a nucleic acid molecule encoding a protein that induces immunity. Suitable antigens are known and available from commercial, government, and scientific sources (see the specification at least at page 11, lines 14-15).

With respect to the statement on page 3 that the pathogen can be any substance causing disease, that is not correct. The claim language must be interpreted in view of the specification and the claim per se. The claims require that the pathogen must have DNA that encodes an antigen that elicits immunity against the pathogen. It is very clear beginning at page 1 that pathogen is an infectious agent, such as a bacteria or virus. Note in particular at page 7, lines 9-12, which states in relevant part "It is therefore an object of the present invention to provide a method and compositions to provide prolonged, improved protection against infectious pathogens, including *P. falciparu*m, *F. Tularensis*, *H. pylori*, and *B. anthraci*, especially using oral or intranasal routes of administration.

Moreover, the specification refers to more than just malaria (pages 23-32) and anthrax (pages 33-34). See page 13, for specific tularemia antigens. Reference to an HIV vaccine and DNA plasmid vector is found at pages 23-24, along with the description of how to make the vector. Other pathogens are described in detail in the background of the invention.

The claims are drawn to a new formulation providing a means for enhancing mucosal delivery of these nucleic acids encoding known antigens. The claims define an improved DNA vaccine formulation generally, not a specific vaccine. Appellants do not claim to have invented DNA vaccines, and indeed have provided much evidence to show that DNA vaccines were known as of the date the application was filed. See, for example, Partidos, et al. *J. Immunol. Method.* 195:135-138 (1996); Pertmer, et al., *Vaccine* 13(15):1427-1430 (1995); Singh, et al., *Pharm. Res.* 8(7):958-961 (1991); Smith, et al., *Oral Microbiol. Immunol.* 15:124-130 (2000); and Thomasin, et al., *J. Control. Rel.* 41:131-145 (1996) (all cited at page 21 of the specification and in the Information Disclosure Statement made of record June 14, 2004). The specification and application instead are drawn to the advantages obtained using the polymeric carrier.

The best evidence against the examiner's rejection is the article cited by the Examiner in the Office Action mailed December 22, 2003, O'Hagan, *J. Pharm. Pharmacol.* 50:1-10 (1997) ("O'Hagan"), a copy of which is enclosed in the Appendix, **dated four years before the priority date of this application**. O'Hagan makes clear that even as of 1997, nucleic acid vaccines, while not being perfect and having some FDA issues, were effective and could be delivered using a polymeric carrier. Additional papers were enclosed with the Amendment and Response filed August 10, 2004 to show that DNA vaccines are considered to be enabled and

vaccination with them does not require "undue experimentation". See Pachuk, et al. *Curr Opin Mol Ther.* 2(2):188-98 (2000); Barnes, et al. *Curr Opin Mol Ther.*, 2(1):87-93 (2000); and Watts and Kennedy, *Int. J. Parasitol.* 29(8):1149-63 (1999) ("Watts"), copies of which are enclosed in the Evidence Appendix. The Examiner pointed to Pachuk, page 188 where it is stated that "DNA vaccine technology is still in its infancy and much research needs to be done to ***improve*** the ***efficiency*** with which these vaccines work in humans" as rebuttal to Appellants use of Pachuck as evidence that DNA vaccines are enabled. Appellants respectfully draw the Examiners attention to the fact that Pachuk is not stating that research needs to be done for DNA vaccines to work, but to improve the efficiency with which they work, which means that they do work. There is no legal requirement for patentability that a high degree of efficiency be obtained, only that what is claimed can or does work. Also, the Examiner quoted from Pachuk at page 195, where it is stated that "it is recognized that one of the major limitations to the success of DNA vaccines is its delivery". This in fact, is the problem the present application seeks to solve (see the specification at least from page 9, line 26 until page 10, line 31). Also quoted by the Examiner was the sentence in Pachuk stating that "it is unclear which cells are to be targeted for optimal eliciting of immune response" (citing Pachuk, page 188). The specification discusses the cells to be targeted at least at page 10, lines 19-31. The Examiner further cited to a summary by McDonnel, et al., Medscape General Medicine, 1(3) (1999) ("McDonnel"), which states many prophetic problems that could arise with DNA vaccines. According to McDonnel and cited by the Examiner, there is no evidence of these problems having occurred (*See* the office action mailed on May 18, 2007, page 5). It is therefore unclear how McDonnel is evidence that

DNA vaccines do not work or are unpredictable. Recitation of potential problems is not evidence of unpredicatability.

The examiner has provided no evidence whatsoever that this method would not work; only unsupported allegation based on the belief that "the claims are very broad" (page 4, Office action mailed on May, 18, 2007; page 3, office action mailed August 7, 2006, in a statement identical to the previous office action). Indeed, having started with the proposition that malarial and anthrax antigens are enabled, the examiner should have based the rejection on why the specification's enablement for these antigens is not sufficient for other antigens.

Applying the *Wands* factors, it is clear from the amount of direction and guidance in the specification that sufficient detail is provided to one of ordinary skill in the art to make and use the claimed composition.

The quantity of experimentation, the state of the prior art, the relative skill of those in the art, and the predictability of the art

The skill of one in the art is high. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The genetic manipulation of plasmid DNA is routine in the art. As described in Watts, plasmid vectors can be rapidly constructed and easily tested. All that is required is the DNA sequence of the antigen. Watts and the specification on pages 4-6 and pages 11-17, for example, disclose a

number of DNA vaccines for bacterial, viral, and parasitic pathogens suitable for use in the claimed formulation of the present application. See also discussion above. Therefore, the creation of numerous, different plasmids encoding antigens from a variety of pathogens would be routine experimentation for one of ordinary skill in the art. In addition, the skill of one in the art with respect to incorporation of active agents into polymers is also high (for example, see page 21, last paragraph). There is also predictability in the art with respect to delivery of vaccines by polymeric particles (for example, see page 20, lines 2-18).

The amount of direction and guidance presented, the presence of working examples, the nature of the invention.

The claims define compositions wherein nucleic acid encoding an antigen is encapsulated in a mucoadhesive controlled release particulate formulation. The specification describes the use of these vaccine compositions to induce an immune response against pathogens such as malaria, anthrax, tularemia, and *H. pylori*. The specification at least at pages 4-6 and pages 11-17, discloses a number of DNA vaccines for bacterial, viral, and parasitic pathogens suitable for use in the claimed formulation of the present application. The specification discloses the encapsulation of DNA in a biodegradable polymer to achieve slow release into the system at least at pages 17-20. Finally, the specification provides ***in vivo*** data in BALB/c mice immunized with vaccine/PLGA (recited in claim 8) particles, PLGA-alone, or a control oligodeoxynucleotide/PLGA particles verifying protective immunity only in mice immunized with the vaccine/PLGA particles (see pages 32-33).

Claim 5 depends on claim 1 and further requires that the composition have a particulate diameter of less than 5 microns. The examiner has provided no basis for the allegation that one would not know how to make a particulate formulation as claimed, and indeed later asserts that the prior art discloses just such a formulation.

Claim 8 adds the further limitation that the polymer in the formulation is a low molecular weight poly(D,L-lactide-co-glycolide) ("PLGA"). These polymers are available from a number of commercial suppliers and approved by the FDA for administration to humans. Claims 1, 5 and 8 are enabled. Indeed, the Board's attention is drawn to Partidos, et al, J. Immunol. Methods. 195:135-138 (1996) which is specific to mucosal immunization with a measles nucleoprotein encapsulated in PLG microparticles, although not as claimed.

Claim 3 is enabled

Mucoadhesives are known in the art, and the specification discloses the addition of a mucoadhesive at least at pages 21-23. The specification exemplifies improved mucoadhesion observed with particles with a mucoadhesive as an added component (*See* the specification from page 22, line 1 until page 23, line 2).

The examiner has provided no basis for alleging one would not know how to make a mucoadhesive formulation. Therefore, claim 3 is enabled.

Claim 4 is enabled

Enteric coatings are routinely used in the pharmaceutical art, can be purchased commercially, and the specification at least at page 23, lines 9-14 provides an example of an enteric coating. It would therefore be routine for a skilled artisan to make a vaccine as defined

by claim 1 including an enteric outer coating or capsule as required by claim 4. Therefore, claim 4 is enabled.

Claims 6 and 7

As defined by claims 6 and 7, the composition can be formed by a method that contains the following steps: (1) lyophilizing a solution of a biodegradable polymer to form an open-celled polymeric foam of approximately 95% void volume, (2) impregnating the foam with an aqueous solution of the nucleic acid, (3) lyophilizing the foam to remove the water, and (4) extruding the resulting matrix at ultrahigh pressures as defined by claim 6 (disclosed least at pages 27-28). Again, the examiner has provided no basis for rejecting this claim other than the allegation that because the claims are "very broad" they must not be enabled.

The specification discloses administration of the vaccines at least at page 32. The specification at least at page 26 describes appropriate size ranges for the particles as defined by claims 5 and 8. Methods for encapsulating nucleic acids into the polymeric foam are disclosed in the specification on page 19. Therefore the specification not only describes how to make and use the claimed formulation, but demonstrates that appellants have actually made and used the formulation.

Claim 9 is enabled

The specification from page 1, line 23 to page 6, line 7 discusses in detail malaria, tularemia, and anthrax, diseases which are caused by *Plasmodium falciparum*, *Francisella tularensis*, and *Bacillus anthracis*, respectively. Antigens to these pathogens are known in the art (see the specification from page 11 to page 17, discussing antigens to the four pathogens

listed in claim 9). It would be routine for a skilled artisan to make a nuclei acid molecule encoding antigens to these pathogens and encapsulate them in a mucoadhesive controlled release formulation, based on the teachings in the specification, for the manufacture of a vaccine formulation for inducing an immune response to the pathogens listed in claim 9. The examiner has already acknowledged that the specification is enabling for two of these three specific pathogens. Therefore, claim 9 is enabled.

Claim 10 is enabled

Adjuvants are known in the art, and the specification at least at page at page 11, lines 17-24 provides examples. It would therefore be routine for a skilled artisan to make a vaccine as defined by claim 1 including adjuvants as required by claim 10, as described in the specification, for the reasons discussed above. Therefore, claim 10 is enabled.

Claim 11 is enabled

Methods for measuring DNA release are known in the art, and are disclosed in the specification at least from page 29, line 18, to page 31, line 28. The specification at least from page 23, line 19, to page 24, line 16, provides an example showing recovery of DNA from PLGA matrices throughout a 6 week incubation period. The examiner has provided no reason why one skilled in the art would not be able to measure DNA release, nor that the formulation of claim 1 would release DNA. Therefore, claim 11 is enabled.

Conclusion

The claims are drawn to vaccine compositions incorporating nucleic acid encoding antigen, such as plasmid DNA, made by encapsulating the DNA within a mucoadhesive

controlled release particulate formulation. The standard for enablement is whether one skilled in the art would be able to make a vaccine composition as claimed. The prior art and specification teach the use of DNA in the production of vaccines against a vast array of diseases. One could routinely substitute these DNA sequences into the vaccine compositions as described in the specification to make a composition to induce an immune response. Appellants are not claiming any unique DNA, but DNA encoding antigens that are present in pathogens when incorporated into a mucoadhesive controlled release particulate formulation. The application clearly provides support for such a formulation, and provides actual working examples.

Claim 9 is not drawn to a broad range of pathogens, but to four specific pathogens. It appears in generalizing the rejection to all of the independent claims that the examiner has failed to individually examine the dependent claims, as required.

(C) Rejections under 35 U.S.C. § 112, second paragraph

Claims 1 and 3-11 was rejected under 35 U.S.C. §112 second paragraph as allegedly being unclear. According to the Examiner, claim 1 recites the limitation "a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particle", and it is unclear if the pathogen itself is encapsulated in the particle or it is the DNA encoding a specific antigen encapsulated in the particle.

Claim 1 is drawn to:

A vaccine composition for inducing an immune response to a pathogen comprising

a nucleic acid encoding an antigen eliciting an immune response to the pathogen

encapsulated in a mucoadhesive controlled release particulate formulation

comprising an open-celled polymeric foam of approximately 95% void volume,

or

particles thereof.

Appellants respectfully submit that one of ordinary skill in the art would understand that the nucleic acid, not the pathogen, is encapsulated into the particle. A claim is interpreted in light of the specification (See MPEP §2111) as well as based on how one of ordinary skill in the art would understand the ordinary language of the claims. It would be clear to one of ordinary skill in the art that the claims do not require using pathogens, dead or alive in the claimed compositions, from the disclosure in the specification. Therefore, claims 1 and 3-11 are clear.

(D) Rejections under 35 U.S.C. § 103(a)

Claims 1 and 3-11 are non-obvious over O'Hagan in view of Mikos.

The Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining

whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

"The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . .there is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."

(*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight '" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964)).

In response to the *KSR* decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "[I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Forcarino to Technology Center Directors (May 3, 2007).

O'Hagan

O'Hagan is a review article discussing the advances in vaccine adjuvants for systemic and mucosal administration ***prior to 1997***. It should be noted that O'Hagan is cited above by Appellants to support enablement of their claims, since O'Hagan describes vaccines, including vaccines made by recombinant DNA technology and nucleic acid based vaccine, as being known and effective no later than 1997, five years before the priority date of this application.

O'Hagan discloses the use of biodegradable polymers as vaccine adjuvants, in particular, the encapsulation of protein antigens into poly(lactide-co-glycolides) microparticles and the use of emulsions formed of materials such as mineral oil, and those which are advantageous for mucosal administration.

Mikos

Mikos discloses polymeric materials used to make a pliable, non-toxic, injectable porous template for vascular ingrowth. The materials disclosed in Mikos are used for tissue engineering and regeneration (Mikos, abstract); not nucleic acid delivery or indeed, vaccine delivery.

Even if one combined O'Hagan with Mikos, one would still not have a vaccine delivery formulation, much less one as claimed.

Claims 1, 5, and 10 are non-obvious over O'Hagan in view of Mikos

O'Hagan does not disclose the claimed composition. Mikos does not make up for this deficiency. While O'Hagan states that delivery of a vaccine composition by mucosal administration would be "ideal" (Table 1, p. 2), the reference does not teach or suggest enhancing antigenicity by increasing mucoadhesion using a porous polymeric matrix or particles thereof.

The Examiner acknowledge that O'Hagan does not disclose or suggest a composition comprising nucleic acid encoding an antigen that is encapsulated in a mucoadhesive controlled release particulate formulation. However, the Examiner alleges that O'Hagan discloses mucosal immunization including nasal and oral (citing O'Hagan, page 4), and that mucoadhesiveness of the formulation will be an inherent property of a microparticle formulated for mucosal delivery. The Examiner has no basis for such a conclusion of inherency. According to the MPEP §2112 (IV), "In relying upon the theory of inherency, the examiner **must** provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17

USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)". The Examiner has not done so. It appears as though the Examiner is stating that just because a composition is intended for mucosal delivery it would automatically have mucoadhesive properties. This in fact is not the case. The specification at least at page 22, lines 21-25 demonstrates little or no adherence to the dome region of murine intestinal loops, of particles consisting of PLGA, with no bioadhesive. There is no disclosure in the prior art of the need for a high void volume within the matrix. **No art has been cited as showing this claimed element.** Thus, a combination of O'Hagan and Mikos does not recite all of the limitations of the claims as required by a rejection under 35 U.S.C. 103(a).

O'Hagan does not disclose a vaccine composition comprising a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume or particles thereof. The Examiner acknowledged this, but provided Mikos to make up for this deficiency. Mikos discloses the use of semicrystalline polymers such as poly(lactic acid-glycolic acid) having a porosity in the range of 50-95% for use in tissue regeneration, which allows vascular ingrowth and the introduction of cells into the matrix without damage to the cells or patient. This is not a drug delivery device, much less one for delivery of nucleic acid. There is no motivation for one of ordinary skill in the art to combine Mikos with O'Hagan as the Examiner has done. The Examiner is not only using impermissible hindsight reconstruction, the Examiner is also not considering the references as a whole (*See* MPEP §2141.02). The legal standard makes it quite clear that it is not sufficient to use that which applicants' claim as a starting point, then searching through the prior art, picking and choosing to find those features

that may be known. The art must lead one of skill to it, i.e., the motivation to combine as applicants have done, with a reasonable expectation of success, must be found in the cited art.

According to the Examiner, one of ordinary skill in the art would have been motivated to replace the biodegradable polymer in O'Hagan with the polymer of 95% void volume taught by Mikos, because O'Hagan discloses that in delivery of antigens by biodegradable polymers including PLG, the particle size is shown to be an important factor affecting immunogenicity (citing O'Hagan, page 6). It is unclear how such a disclosure by O'Hagan would motivate one of ordinary skill in the art to combine O'Hagan and Mikos to arrive at the claimed composition, which does not recite particle size, and particularly as it was cited as it relates to void volume. There is simply no disclosure of why one needs mucoadhesion and a very high void volume matrix to be used for delivery of nucleic acid vaccines.. The Examiner has provided no reason why one of ordinary skill in the art would combine O'Hagan and Mikos to arrive at the claimed composition. The Examiner has focused his analysis on the obviousness of the differences of the claimed composition with the prior art, instead of on the obviousness of the claimed composition as a whole. Not only does the prior art either alone or in combination recite all of the limitations of the claims, there would be no motivation for one of ordinary skill in the art to combine Mikos and O'Hagan as the Examiner has done. Therefore, claims 1, 5, and 10 are non-obvious over O'Hagan in view of Mikos.

Claim 3 is non-obvious over O'Hagan in view of Mikos

Claim 3 requires that the composition of claim 1 further comprise a mucoadhesive polymer coating. As previously discussed, O'Hagan does not disclose the encapsulation of DNA

in a mucoadhesive controlled release particulate formulation, nor that the composition further comprise a mucoadhesive. Mikos does not disclose a formulation comprising an open-celled foam for encapsulating nucleic acid, which further comprises a mucoadhesive polymer coating. No art has been cited as disclosing PLGA as a mucoadhesive polymer. Thus the prior art in combination neither recites all of the limitations of the claims as required by a rejection under 35 U.S.C. §103(a), nor suggests a desirability of the combination as the Examiner has done. Therefore, claim 3 non-obvious over O'Hagan in view of Mikos.

Claim 4 is non-obvious over O'Hagan in view of Mikos

Claim 4 requires the composition of claim 1 further comprise an enteric outer coating or capsule. O'Hagan does not disclose or suggest a composition for inducing an immune response to a pathogen, that comprises an open-celled polymeric foam of approximately 95% void volume or particles thereof, and further comprises an enteric outer coating or capsule as recited in claim 4. Mikos does make up for this deficiency. Thus the prior art in combination neither recites all of the limitations of the claims as required by a rejection under 35 U.S.C. §103(a), nor suggests a desirability of the combination as the Examiner has done. Therefore, claim 4 is novel over O'Hagan and Perez.

Claim 9 is non-obvious over O'Hagan in view of Mikos

Claim 9 recites all of the limitations of claim 1 and requires that the pathogen be *Plasmodium falciparum, Francisella tularensis, Bacillus anthracis* and *Helicobacter pylori.* For discussed with respect to claims 1, 5, and 8, O'Hagan does not disclose a composition for

inducing an immune response to any of the pathogens listed in claim 9. Mikos does not make up for this deficiency. Therefore, claim 9 non-obvious over O'Hagan in view of Mikos.

Claim 11

None of O'Hagan or Mikos, alone or in combination, disclose or suggest release of antigen over a period of weeks to months from an open celled foam. Accordingly, claim 11 is non-obvious over O'Hagan in view of Mikos.

(F) Summary

Claims 1 and 3-11 are enabled and in compliance with the requirements of 35 U.S.C. 112. One of skilled in the art would be able to make and use the claimed compositions from the description Appellants have provided and Appellants have demonstrated they were in possession of the claimed subject matter at the time this application was filed.

Claims 1 and 3-11 are clear and are therefore in compliance with 35 U.S.C. 112, since the standard is whether one skilled in the art would understand the meaning of the claim, not whether it could be stated more articulately.

Claims 1 and 3-11 are non-obvious over the cited art, O'Hagan and Mikos, since neither O'Hagan nor Mikos, either alone or in combination, disclose each and every claimed limitation. Moreover, even if the references in combination disclosed each claimed limitation, there is no motivation to modify and combine as appellants have done, with a reasonable expectation of success in long term release of antigen.

Accordingly, allowance of claims 1 and 3-11 is earnestly solicited.

Respectfully submitted,

/ Patrea L. Pabst /

Patrea L. Pabst
Reg. No. 31,284

Date: August 20, 2007

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)

Claims Appendix: Claims On Appeal

1. A vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof.

3. The composition of claim 1 further comprising a mucoadhesive polymer coating.

4. The composition of claim 1 further comprising an enteric outer coating or capsule.

5. The composition of claim 1 having a particulate diameter of less than five microns.

6. The composition of claim 1 formed by

lyophilizing a solution of a biodegradable polymer to form an open-celled polymeric foam of approximately 95% void volume,

impregnating the foam with an aqueous solution of the nucleic acid,

lyophilizing the foam to remove the water, and

extruding the resulting matrix at ultrahigh pressures.

7. The composition of claim 1 wherein the method further comprises cryogenically grinding the matrix to an average particle size of fifteen microns in diameter; and

sieving to isolate particles less than five microns in diameter.

8. The composition of claim 1 wherein the polymer is a low molecular weight poly(D,L-lactide-co-glycolide).

9. The composition of claim 1 wherein the pathogen is selected from the group consisting of *Plasmodium falciparum*, *Francisella tularensis*, *Bacillus anthracis*, and *Helicobacter pylori*.

10. The composition of claim 1 further comprising providing an adjuvant with the antigen.

11. The composition of claim 1 wherein the antigen is expressed or released for a period of weeks to months.

Evidence Appendix

Evidence cited by the Examiner in office action dated December 22, 2003

O'Hagan, *J. Pharm. Pharmacol.*, 50:1-10 (1997).

Evidence submitted with Amendment and Response filed August 10, 2004

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Partidos, et al. *J. Immunol. Method.* 195:135-138 (1996)

Pertmer, et al., *Vaccine* 13(15):1427-1430 (1995)

Singh, et al., *Pharm. Res.* 8(7):958-961 (1991)

Smith, et al., *Oral Microbiol. Immunol.* 15:124-130 (2000)

Thomasin, et al., *J. Control. Rel.* 41:131-145 (1996)

Related Proceedings Appendix

None